



EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of a health claim related to *Vitis vinifera* L. seeds extract and maintenance of normal venous blood flow pursuant to Article 13(5) of Regulation (EC) No 1924/2006

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to *Vitis vinifera* L. seeds extract and maintenance of normal venous blood flow pursuant to Article 13(5) of Regulation (EC) No 1924/2006¹

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)^{2, 3}

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from Nutrilinks Sarl, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Belgium, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to *Vitis vinifera* L. seeds extract and maintenance of normal venous blood flow. The Panel considers that the food constituent, which is the subject of the health claim, is sufficiently characterised. The claimed effect, maintenance of normal venous blood flow, is a beneficial physiological effect. The applicant identified two human intervention studies as pertinent to the health claim. Owing to the very limited information provided in relation to one study, and that the second study was conducted with a food not complying with the characterisation of the food which is the subject of the health claim and did not measure venous blood flow, the Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claim. The Panel concludes that a cause and effect relationship has not been established between the consumption of *Vitis vinifera* L. seeds extract and maintenance of normal venous blood flow.

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KEY WORDS

Vitis vinifera, venous blood flow, health claims

¹ On request from the Competent Authority of Belgium following an application by Nutrilinks Sarl, Question No EFSA-Q-2012-00387, adopted on 28 November 2012.

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SUMMARY

Following an application from Nutrilinks Sarl, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Belgium, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to *Vitis vinifera* L. seeds extract and maintenance of normal venous blood flow.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.

The food constituent that is the subject of the health claim is an extract of *Vitis vinifera* L. seeds which is standardised by its content of polyphenols. The Panel considers that *Vitis vinifera* L. seeds extract is sufficiently characterised.

The claimed effect proposed by the applicant is “contributes to promote venous circulation in the legs”. The target population proposed by the applicant is healthy adults in the general population. From the information provided by the applicant, the Panel notes that the claimed effect relates to the maintenance of venous blood flow, which can be assessed *in vivo* by standard dynamic ultrasound techniques. The Panel considers that maintenance of normal venous blood flow is a beneficial physiological effect.

The applicant identified two human intervention studies as pertinent to the health claim.

A randomised, double-blind, placebo-controlled, multicentre intervention study investigated the effect of grape seed extract (GSE) on signs and symptoms of chronic venous insufficiency (CVI) in women with leg swelling gradually appearing during the day (evening swelling), and with a thickening of the subcutaneous tissue of at least 6 mm. Women were randomised to consume either 150 mg/day of GSE (n=46) or placebo (n= 49) for two months. The study population was not adequately characterised in relation to CVI, no data/rationale for extrapolating the results obtained in the study group (subjects with evening leg swelling and thickening of the leg’s subcutaneous tissue) to the target population (healthy subjects without evening leg swelling and thickening of the leg’s subcutaneous tissue) for the claim have been provided, and no data have been provided with respect to the outcome measures of interest (e.g. vein diameters, venous refluxes). Owing to the very limited information provided in relation to this study, the Panel considers that no conclusions can be drawn for the scientific substantiation of the claim.

A randomised, double-blind study investigated the effect of a blend of pomace and grape seeds on “leg heaviness”, leg pain, night cramps, paresthesias and night oedema. The information provided regarding the characterisation of the study product is insufficient to ensure that this product complies with the specifications provided for the food constituent, *Vitis vinifera* L. seeds extract, which is the subject of the health claim. Venous blood flow was not measured. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

The Panel notes that no studies from which conclusions could be drawn for the scientific substantiation of the claim were provided by the applicant.

The Panel concludes that a cause and effect relationship has not been established between the consumption of *Vitis vinifera* L. seeds extract and maintenance of normal venous blood flow.

TABLE OF CONTENTS

Abstract	1
Summary	2
Table of contents	3
Background	4
Terms of reference.....	4
EFSA Disclaimer.....	4
Information provided by the applicant	6
Assessment	6
1. Characterisation of the food/constituent.....	6
2. Relevance of the claimed effect to human health	7
3. Scientific substantiation of the claimed effect.....	7
Conclusions	9
Documentation provided to EFSA	9
References	9
Glossary/Abbreviations	11

BACKGROUND

Regulation (EC) No 1924/2006⁴ harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Article 13(3) shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

STEPS TAKEN BY EFSA

- The application was received on 06/03/2012.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.
- On 30/03/2012, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
- On 21/05/2012, EFSA received the missing information as submitted by the applicant.
- The scientific evaluation procedure started on 31/05/2012.
- On 12/09/2012, the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application. The clock was stopped on 21/09/2012 and restarted on 06/10/2012, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
- On 17/10/2012, EFSA received the requested information (which was made available to EFSA in electronic format on 05/10/2012).
- During its meeting on 28/11/2012, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to *Vitis vinifera* L. seeds extract and maintenance of normal venous blood flow.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to: *Vitis vinifera* L. seeds extract and maintenance of normal venous blood flow.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of *Vitis vinifera* L. seeds extract, a positive assessment of its safety, nor a decision on whether *Vitis*

⁴ Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

vinifera L. seeds extract is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: Nutrilinks Sarl, Chemin de Beau-rivage 7, Post code 96 CH-1000 Lausanne 21, Switzerland.

Food/constituent as stated by the applicant

According to the applicant, the food constituent that is the subject of the health claim is grape seed extract.

Health relationship as claimed by the applicant

According to the applicant, the health claim is “contributes to promote venous circulation in the legs”. The applicant claims that the grape seed extract, which contains polyphenols and mainly oligomeric proanthocyanidins, may contribute to improve venous microcirculation by its effects on venous vein walls.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: “contributes to promote venous circulation in the legs”.

Alternative wordings: “helps to decrease feeling of heavy legs”, “helps to decrease feeling of tired legs”, “helps reduce the discomfort associated with tired legs”.

Specific conditions of use as proposed by the applicant

According to the applicant, 120 to 150 mg per day of grape seed extract should be consumed during a meal. The applicant has proposed healthy adults in the general population as the target population.

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claim is an extract of *Vitis vinifera* L. seeds.

Vitis vinifera L. (grape vine) is a perennial plant, originating from North and South Africa or South West Europe, which belongs to the *Vitaceae* family. The dry powder extract is obtained by extraction of seeds of *Vitis vinifera* L. with ethanol and ethyl acetate, and subsequent evaporation, filtration, concentration and spray-drying. The extract of *Vitis vinifera* L. seeds is standardised by its content of specific polyphenols: at least 35 % of gallic acid, catechins, epicatechins and procyanidin dimers B1, B2, B3 and B4. Procyanidin dimers account for at least 7 % of the extract. These constituents can be analysed in foods by established methods.

Upon EFSA's request for additional information, the applicant clarified that the range given for the plant/extract ratio depended on the amount of polyphenols in the plant used to obtain the extract.

Information pertaining to the manufacturing process, control specifications and batch-to-batch variability has been provided by the applicant.

The dry powder extract of *Vitis vinifera* L. seeds is proposed to be used in food supplements, with no reference to any specific formulation, in a quantity of 120-150 mg of extract per serving.

The Panel considers that the food constituent, *Vitis vinifera* L. seeds extract, which is the subject of the health claim, is sufficiently characterised.

2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is “contributes to promote venous circulation in the legs”. The target population proposed by the applicant is healthy adults in the general population.

Upon EFSA’s request for clarification, the applicant stated that “venous circulation in the legs can be measured by changes in venous reflux measurements evaluated by echo Doppler”.

From the information provided by the applicant, the Panel notes that the claimed effect relates to the maintenance of normal venous blood flow. Blood flow in blood vessels, including the veins, can be assessed *in vivo* by standard dynamic ultrasound techniques (e.g. echo Doppler).

The Panel considers that the health claim refers to the maintenance of normal venous blood flow in healthy adults without signs or symptoms of chronic venous insufficiency (CVI) and does not include the treatment of CVI.

The Panel considers that maintenance of normal venous blood flow is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

The applicant performed a literature search in Science Direct, PubMed/Medline, Scirus, Mary Ann Liebert, SpringerLink, Wiley Interscience, Google Scholar, and Google, complemented by hand search, using search terms [(“grape seed extract” OR “grapeseed extract” OR “*Vitis vinifera*” OR “polyphenols” OR “procyanidolic oligomers” OR “oligomeric proanthocyanidins” OR “procyanidin” OR “proanthocyanidin”) AND (“venous circulation” OR “chronic venous insufficiency” OR “oedema” OR “swollen legs” OR “heavy legs” OR “leg health”)] in studies published after 1990. Studies were included if they were undertaken with 120-150 mg of grape seed extract or 45-52.5 mg of grape seed polyphenols in women showing symptoms of chronic venous insufficiency of the lower limbs, including swelling of the legs as a symptom and oedema as a clinical sign. Open clinical trials and studies carried out with people belonging to the C5 or C6 class in the CEAP (Clinical-Etiology-Anatomy-Pathophysiology) classification were excluded.

The applicant identified two human intervention studies (Allaert, 2009, unpublished; Djian et al., 2006) as pertinent to the health claim.

In a randomised, double-blind, placebo-controlled, multicentre intervention study, Allaert (2009, unpublished) investigated the effect of a grape seed extract (GSE) on signs and symptoms of CVI in women (aged 18-75 years; BMI 20-30 kg/m²) with leg swelling gradually appearing during the day (evening swelling) up to at least 50 cm³, and with a thickening of the subcutaneous tissue of at least 6 mm. The Panel notes that the GSE used complies with the specifications of the *Vitis vinifera* L. seeds extract which is the subject of the health claim. Each practitioner was asked to enrol nine women in the study. Exclusion criteria were leg swelling with an ankle circumference >28 cm, leg swelling already present in the morning, leg swelling of cardiac or renal aetiology or in relation to the menstrual cycle, any previous surgery for venous insufficiency, presence of a healed or open ulcer, current treatment (or treatment in the previous month) with calcium blockers, “venoactive drugs”, non-steroidal anti-inflammatory drugs, oral corticosteroids (inhaled form was accepted), vasoactive drugs, diuretics, or elastic compression. Analgesics, preferably paracetamol, were occasionally allowed provided that the consumption of such was reported.

The Panel noted that the women recruited presented signs and symptoms of CVI, such as leg swelling and changes in subcutaneous tissue, and thus requested the applicant to clarify the characterisation of the subjects recruited in relation to disease status (e.g. CEAP classification of CVI), as well as to

provide data/rationale for extrapolating the results obtained in the study group (subjects with CVI) to the target population (healthy subjects without CVI) for the claim. The applicant stated that the subjects recruited for the study had no diagnosis of CVI, as they only presented with leg swelling but not oedema. However, the Panel notes that the applicant did not provide adequate characterisation of the study population in relation to CVI, that leg swelling is an alternative wording for peripheral oedema, which was the primary outcome of the study, and that changes in subcutaneous tissue (e.g. a thickening of the subcutaneous tissue of at least 6 mm) correspond to class C4 in the CEAP classification of CVI. The Panel also notes that no data/rationale for extrapolating the results obtained in the study group (subjects with evening leg swelling and thickening of the leg's subcutaneous tissue) to the target population (healthy subjects without evening leg swelling and thickening of the leg's subcutaneous tissue) for the claim were provided by the applicant.

Women were randomised to consume either 150 mg/day of GSE (n=46) or placebo (calcium hydrogen phosphate dihydrate and silicified microcrystalline cellulose; n= 49) for two months. The Panel is unclear on the methods used for recruitment and randomisation owing to the very limited information provided by the applicant following EFSA's request for clarification on these points. Before and after the two-month treatment period, women were examined by an angiologist who assessed the oedema leg volume by measuring the leg circumferences at the tibial malleolar level, and 10 and 20 cm above, and the oedema thickness at the same levels using duplex Doppler according to a specific protocol. The primary outcome of the study was the percentage of women experiencing a reduction of oedema >50 %. The great saphenous and popliteal vein diameters and venous refluxes (measured with duplex Doppler), and symptoms such as leg pain and heaviness, pruritus, paresthesia and cramps (measured through visual analogue scales) were also assessed before and after the intervention.

Upon a second EFSA request for clarification on the appropriate outcome measures for assessing the claimed effect, the applicant stated that oedema leg volumes and leg circumferences at the tibial malleolar level are appropriate outcome measures of the claimed effect, whereas the symptoms described above are not direct measures of venous blood flow. The Panel considers that changes in oedema leg volumes and leg circumferences are not direct measures of venous blood flow, but rather estimations of water accumulation in the extra-vascular space, which may be influenced by factors other than venous blood flow.

The author states that the diameter of the great saphenous vein and the frequency and duration of the venous reflux remained stable during the study, and that no significant differences were observed between groups.

The Panel notes that no data in the application or following an explicit request by EFSA were provided with respect to these outcome measures of interest. Owing to the very limited information (e.g. insufficient characterisation of the study population in relation to CVI, lack of evidence for extrapolating the results from the study population (subjects with evening leg swelling and thickening of the leg's subcutaneous tissue) to the target population (healthy subjects without evening leg swelling and thickening of the leg's subcutaneous tissue), and lack of data with respect to the appropriate outcome measures of the claimed effect) provided in relation to this study, the Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

Djian et al. (2006) conducted a two-month, randomised, double-blind study in 108 women (mean age 43 ± 13.4 years; mean body weight 62.4 ± 11.00 kg; "leg heaviness" 62.2 mm, measured on a 0-100 mm visual analogue scale (VAS)) who received 6 (n=36) or 3 (n=38) pills of a blend of pomace and grape seeds (corresponding to 90 mg or 45 mg of polyphenols, respectively), or identical placebo pills (number and composition unknown; n=34). The study product is titrated to 21.5 % of total polyphenols (catechins, epicatechins, epicatechin-3-O-gallate, B1, B2, B3 and B4 oligomers, and gallic acid).

Upon EFSA's request for clarification of the study product, the applicant indicated that the study product was not the same as the grape seed extract that is the subject of the claim, but it provided the same quantity of polyphenols.

"Leg heaviness", leg pain, night cramps, paresthesias and night oedema were assessed with verbal and visual analogue scales at day 0 and at the end of the first and second month of treatment.

Upon EFSA's request for clarification on how these outcome measures related to the claimed effect, the applicant indicated that leg heaviness and pain, night cramps, oedema and paresthesias are not direct measures of venous blood flow but could be used in support of the claimed effect.

The Panel notes that the information provided regarding the characterisation of the study product is insufficient to ensure that this product complies with the specifications provided for the food constituent, *Vitis vinifera* L. seeds extract, which is the subject of the health claim. The Panel also notes that venous blood flow was not measured in this study. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

The Panel notes that no studies from which conclusions could be drawn for the scientific substantiation of the claim were provided by the applicant.

The Panel concludes that a cause and effect relationship has not been established between the consumption of *Vitis vinifera* L. seeds extract and maintenance of normal venous blood flow.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food constituent, *Vitis vinifera* L. seeds extract, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect proposed by the applicant is "contributes to promote venous circulation in the legs". The target population proposed by the applicant is healthy adults in the general population. Maintenance of normal venous blood flow is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of *Vitis vinifera* L. seeds extract and maintenance of normal venous blood flow.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on *Vitis vinifera* L. seeds extract and maintenance of normal venous blood flow pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0342_BE). March 2012. Submitted by Nutrilinks Sarl.

REFERENCES

Allaert FA, 2009 (unpublished). Randomised, double-blind, placebo-controlled clinical trial of a daily intake of 150 grape-seed extract on women leg swellings.

Djian B, Maillet P, Maurette JM and Bejot M, 2006. Evaluation de l'amélioration symptomatique et de la tolérance d'oenobiol aquadrainant® chez les femmes présentant une symptomatologie de “jambes lourdes” (Evaluation of the symptomatic improvement and the tolerance of oenobiol aquadrainant® in women with a symptomatology of “heavy legs”). *Angéiologie*, 58, 53-59.

GLOSSARY/ABBREVIATIONS

CEAP	Clinical-Etiology-Anatomy-Pathophysiology
CVI	Chronic venous insufficiency
GSE	Grape seed extract
VAS	Visual analogue scale